

REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claim 2 is currently being amended. Support for amended claim 2 may be found in the original claims and specification as filed.

Claims 10-12, 14-21 are requested to be cancelled without prejudice to further prosecution on the merits.

Claims 22-24 are being added. Support for new claims 22-24 may be found in the original claims and specification as filed.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 1-9, 13, and 22-24 are now pending in this application.

35 U.S.C. § 112, second paragraph

In the Office Action, the Examiner rejected claims 1-9, 13, 14, and 17 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In

particular, the Examiner rejected claims 1-9, 13, 14, and 17 for reciting "a nonhydrolyzable nucleotide co-factor the number of molecules which...", because the Examiner asserts that "[i]t is not clear what is encompassed by the term 'the number of molecules of the cofactor.'" Applicants respectfully traverse the rejection. Even if a mixture of three different compounds, each of differing concentration, is used as a component of the nonhydrolyzable nucleotide cofactor, it is clear from the description in the specification that the term "the number of molecules of the cofactor" in the claims refers to the number of molecules of the cofactor finally formed in the reaction solution. Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

The Examiner also rejected claims 14 and 17 for "insufficient antecedent basis." Applicants have cancelled claims 14 and 17 rendering the rejection moot.

35 U.S.C. § 102

The Examiner rejected claims 1, 2, 4-9, and 17 under 35 U.S.C. § 102(b) as being anticipated by Kigawa *et al.* (WO 98/08975), as evidenced by Sena *et al.* (U.S. Patent No. 5,670,316). Applicants respectfully traverse the rejection for the following reasons.

First, the numeric ranges presented in Kigawa *et al.* (page 14, lines 15 to 28 and page 17, lines 2 to 5), are derived from information presented in the list of references cited by Kigawa *et al.* (See references cited at Kigawa *et al.*, page 14, lines 17 to 24). However, Kigawa *et al.* merely recite concentration ranges of RecA-like recombinase and nonhydrolyzable nucleotide cofactor that might possibly be used in a reaction. Simply citing these ranges is not an indication that a RecA-like

recombinase/single-stranded nucleic acid probe complex can be prepared by arbitrarily combining a potential concentration of RecA-like recombinase and a potential concentration of nonhydrolyzable nucleotide cofactor.

Nonetheless, the Examiner asserted that the claims are anticipated by selecting particular values included within the ranges disclosed by Kigawa *et al.* For instance, the Examiner combined the lowest concentration of nonhydrolyzable nucleotide cofactor (0.01 mM ATP γ S) and the highest concentration of RecA-like recombinase (0.025 mM RecA protein), as disclosed by Kigawa *et al.* (page 14, lines 15 to 28 and page 17, lines 2 to 5). Taken as such, the Examiner calculated that the ratio "ATP γ S/RecA protein = 0.4." The Examiner then concluded that this value is formally included in the range of the present invention, as recited in claim 1 of the present specification, and hence rejected the claim as anticipated by Kigawa *et al.*

However, by combining the highest concentration of nonhydrolyzable nucleotide cofactor disclosed by Kigawa *et al.* (5 mM GTP γ S) and the lowest concentration of RecA-like recombinase (0.002 mM RecA protein), a ratio of 2500 is achieved, which is outside of the claimed range. Selecting concentrations as such, Kigawa *et al.* can be argued to disclose ratios of nonhydrolyzable nucleotide cofactor and RecA-like recombinase that range from 0.4 to 2500. In contrast, the pending claims recite a ratio of nonhydrolyzable nucleotide cofactor and RecA-like recombinase that is 10 or less. Therefore, selecting concentrations as such, Kigawa *et al.*'s disclosed range can only, at best, be argued to overlap the recited range.

Under MPEP § 2131.03, "a specific example in the prior art which is within a claimed range anticipates the range." As noted above, Kigawa *et al.*'s disclosed range can only, at best, be argued to overlap the claimed ranges. Further, the ranges and ratios described above are not specific examples. However, the Examiner asserts that

Kigawa *et al.* does include a specific example that anticipates the range, *i.e.*, “specific reaction mixture, No. 23 (Table 1, page 26), which contained 1 ng of 275 bp homologous probe, 500 ng of λ DNA fragments and 15 μ g of RecA.” For this reaction mixture, the Examiner asserted that “[t]he reaction volume was 9 μ l and contained 0.3 mM GTP γ S (page 23, lines 7-17).” The Examiner calculated the RecA concentration as 0.044 mM (assuming a RecA molecular weight of 37,842 as evidenced by Sena *et al.* col. 2, lines 42, 43) and the concentration of the homologous 275 bp probe as 0.011 μ M (assuming a molecular weight of 330 per nucleotide). As such, the Examiner asserted that “the molar ratio of GTP γ S to RecA is 6.8, which is less than 10-fold, and the molar ratio of GTP γ S to nucleotide residue in the nucleic acid probe is 27,000, which is more than 25% of the number of nucleotide residues in the homologous probe.” The Examiner asserted that this example anticipated the rejected claims.

Applicants respectfully disagree that specific reaction mixture, No. 23, anticipates the claimed range. First, Applicants note that the claims do not presume the use of GTP γ S as the nonhydrolyzable nucleotide cofactor. In addition, Applicants respectfully contend that the Examiner’s calculation is incorrect with regard to the ratio of GTP γ S to RecA and the ratio of GTP γ S to nucleotide residues in the nucleic acid probe. The Examiner asserted that the volume of reaction mixture, No. 23 was 9 μ l. However, Applicants respectfully note that the volume of reaction mixture, No. 23 was 18 μ l, (page 24, lines 1-2), because the 9 μ l reaction mixture disclosed in Example 2.1.A.(a) (page 23, lines 6-18) was added to the 9 μ l reaction mixture disclosed in Example 2.1.A.(b) (page 23, lines 19 to page 24, line 2) to give a 18 μ l total reaction mixture. Therefore, reaction mixture, No. 23 has a RecA protein concentration of 0.022 mM and a GTP γ S/RecA protein ratio of approximately 13.7, which is not within

the claimed range. All other examples in Table 1 have lower concentrations of RecA protein than reaction mixture, No. 23, and hence, all these examples have GTP γ S/RecA protein ratios that are higher than the claimed range. Further, the examples in Table 3 and Table 5 have lower concentrations of RecA and higher concentrations of GTP γ S than reaction mixture, No. 23, and hence all these examples have GTP γ S/RecA protein ratios that are higher than the claimed range. Therefore, Applicants respectfully contend that Kigawa *et al.* does not include a specific example that anticipates the claimed range.

Under MPEP § 2131.03:

When the prior art discloses a range which touches, overlaps or is within the claimed range, but no specific examples falling within the claimed range are disclosed, a case by case determination must be made as to anticipation. In order to anticipate the claims, the claimed subject matter must be disclosed in the reference with ***"sufficient specificity to constitute an anticipation under the statute."*** What constitutes a "sufficient specificity" is fact dependent. ***If the claims are directed to a narrow range, the reference teaches a broad range, and there is evidence of unexpected results within the claimed narrow range,*** depending on the other facts of the case, ***it may be reasonable to conclude that the narrow range is not disclosed with "sufficient specificity" to constitute an anticipation of the claims. The unexpected results may also render the claims unobvious.*** (*Emphasis added*).

Applicants respectfully contend that Kigawa *et al.* does not disclose the claimed subject matter with "sufficient specificity" for the following reasons. The pending claims recite a ratio of nonhydrolyzable nucleotide co-factor to RecA-like recombinase of 10 or less. In contrast, as described above, Kigawa *et al.* can be argued to disclose ratios of GTP γ S/RecA that range from 0.4 to 2500. Also as noted above, Applicants contend that Kigawa *et al.* does not include a specific example that anticipates the claimed range.

Further, using ratios as recited in the claimed range, Applicants obtained unexpected results. At the time of filing, from the point of view of reaction efficiency, the reaction was commonly performed with a large excess of ATP_γS relative to RecA. As such, the concept of improving reaction efficiency by reducing the amount of nonhydrolyzable nucleotide cofactor in the reaction system relative to RecA was unexpected, and in fact, was contrary to common practice. In particular, one skilled in the art would not expect that using ratios of nonhydrolyzable nucleotide co-factor relative to RecA-like recombinase of 10 or less would improve reaction efficiency. For these reasons, Applicants respectfully contend that the claims are not anticipated or made obvious by the teachings of Kigawa *et al.* as evidenced by Sena *et al.* Applicants request that the Examiner reconsider and withdraw the rejection.

35 U.S.C. § 103

The Examiner rejected claim 3 under 35 U.S.C. § 103, as being unpatentable over Kigawa *et al.* and Sena *et al.* In addition, the Examiner rejected claims 13 and 14 under 35 U.S.C. § 103 as being unpatentable over Kigawa *et al.* and Kigawa-2 *et al.* (EP 0 687 738 A1). Claim 14 has been cancelled rendering the rejection moot. Claims 3 and 13 depend from claim 1 and include the limitation, "a nonhydrolyzable nucleotide co-factor the number of molecules of which is ... 10 times or less the number of molecules of the RecA-like recombinase." For the reasons discussed above, Applicants respectfully contend that the combination of Kigawa *et al.* and Sena *et al.* does not teach or suggest all the limitations of claim 3, and the combination of Kigawa *et al.* and Kigawa-2 *et al.* does not teach or suggest all the limitations of claim 13. As such,

Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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